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ORIGINAL ARTICLE

Evaluation of Spot Urinary Albumin–Creatinine Ratio as Screening Tool in Prediction of Pre-eclampsia in Early Pregnancy

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Abstract

Objective The aim of this study was to establish whether a spot urinary albumin/creatinine ratio (ACR) measured between 20 and 28 weeks of gestation can predict subsequent pre-eclampsia in asymptomatic pregnant women.

Design Prospective observational study.

Subjects The patients included sixty-two women with singleton pregnancy, normal renal function and no evident proteinuria, attending antenatal clinics between 20 and 28 weeks of gestation in a tertiary care hospital.

Methods The ACR was determined from midstream urine sample taken between 20 and 28 weeks of gestation. Estimation of albumin was done by immunoturbidimetric microalbumin method and creatinine by modified Jaffe's method.

Results Incidence of pre-eclampsia in the study group was 12.90%. The cut-off value for ACR was taken as 35.5 mg/mol. The mean ACR in normotensive group was 19.26 ± 7.99, and in pre-eclampsia group it was 51.95 ± 18.78. For pre-eclampsia, screening in early pregnancy, spot ACR cut-off $\geq$35.5 mg/mol has sensitivity of 87.5%, specificity of 96.30%, PPV of 77.78% and NPV of 98.11%.

Conclusions Spot urinary ACR values are higher in asymptomatic women in early pregnancy, who developed pre-eclampsia later on. When measured early in the second trimester, an ACR $\geq$ 35.5 mg/mmol predicted pre-eclampsia well before the onset of clinical manifestations with high sensitivity and specificity. It can be used as a good screening tool for predicting pre-eclampsia in early pregnancy.

Keywords Albumin · Creatinine · Pregnancy · Pre-eclampsia

Introduction

Pre-eclampsia (PE) is defined as a pregnancy-specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial dysfunction [1]. It is the second highest cause of maternal mortality, constituting 12–18% of pregnancy-related deaths [1]. In developing nations, the incidence of the disease is reported to be 4–18% [2]. Although there is no established preventative therapy, there is still a potential benefit in being able to identify the women at risk, so that appropriate monitoring can be done. There is some evidence to support the prophylactic benefit of the early introduction of aspirin [3], calcium and heparin in such high-risk women [4]. Pre-eclampsia is diagnosed when the blood pressure is at or above 140/90 mmHg occurring on two occasions at least 6 h apart, associated with proteinuria greater than 300 mg/24 h after 20 weeks of gestation [5]. One of the early pathophysiological hallmarks in pre-eclampsia is endothelial cell damage [6]. Microalbuminuria is a marker of endothelial dysfunction and is associated with hypertension, obesity, diabetes and renal disease [7].

Persistent microalbuminuria indicates a high probability of damage of the glomerular filtration capacity of the kidney and is of major diagnostic importance in pregnancy as a possible predictor of developing PE. Although the 24-h collection of urine is the gold standard for quantifying urinary albumin excretion, it is cumbersome and results in a delay of at least 24 h in diagnosis [8]. Many previous studies have measured microalbuminuria in an attempt to predict pre-eclampsia in early pregnancy, postulating that the stage of gross proteinuria is preceded by the stage of microalbuminuria. This study is an attempt to evaluate the role of single spot urinary albumin/creatinine ratio as prediction of pre-eclampsia in asymptomatic pregnant women in early pregnancy.

Materials and Methods

This was a prospective observational study of sixty-two women with singleton pregnancies attending an antenatal clinic at a tertiary care hospital in Institute of Kidney Diseases and Research Centre, Ahmedabad, for routine antenatal care, between 20 and 28 weeks of gestation. The study was approved by the institutional ethical committee, and written informed consent was obtained from all participating women. Inclusion criteria were women over 18 years of age, singleton pregnancy and nil proteinuria upon measurement with a dipstick. Women with haematuria, dipstick-positive proteinuria, ongoing urinary tract infection, multiple pregnancy, acute renal failure, chronic kidney disease (CKD), poor obstetric history, chronic hypertension and diabetes were excluded from the study. Data regarding demographic profile, blood pressure, body mass index (BMI), medical and family history (history of chronic hypertension, diabetes mellitus and CKD) were recorded. Obstetric history was documented regarding gravidity, parity, past history of pre-eclampsia, prematurity, small for gestational age and miscarriage.

All women were clinically evaluated at the booking visit to rule out any risk factor for the development of pre-eclampsia. Blood pressure was measured in the semi-recumbent posture with a left lateral tilt, in the right arm. A spot midstream urine sample was collected for estimation of albumin by immunoturbidimetric microalbumin method and creatinine by modified Jaffe's method in ERBA XL640 fully automatic biochemistry analyser with commercially available reagents. All these women were followed up till

delivery. At each visit, their blood pressure was measured and they were evaluated for the development of any signs and symptoms of pre-eclampsia such as oedema, nausea, vomiting, epigastric pain, decreased urine output and visual disturbances.

Pre-eclampsia was defined as hypertension with blood pressure (BP) of more than or equal to 140/90 mmHg by using Korotkoff 5th sound for diastolic BP associated with proteinuria. Based on these criteria, the women studied were categorized as those who developed pre-eclampsia and those who remained normotensives. The cut-off value of ACR (mmol of albumin/mg of creatinine) was taken as 35.5 mg/mmol as in previous study done by Baweja et al. [9]. ACR was calculated and those with a ratio equal to or more than 35.5 mg/mmol were considered as test positive. Those with a ratio of less than 35.5 mg/mmol were considered as test negative.

Statistical Analysis

The statistical analysis of the data obtained in the present study was carried out using the Statistical Packages for the Social Sciences (SPSS version 20). Normally distributed data were presented as mean and standard deviation, whereas skewed data were expressed as median and range. Independent student's *t* test and Mann–Whitney test have been used to carry out the significant value. Pearson coefficient (*P* value) <.0001 was considered as significant.

Results

A total of 62 women were included in the study group. The mean age of the patients included in the study was 27.79 ± 4.79 years. Thirty-five (56.45%) patients were primipara and 27 (43.54%) were multipara. The mean BMI was 27.6 ± 5.4 kg/m^2. Incidence of pre-eclampsia in the study group was 12.90%. At the time of delivery, the mean systolic blood pressure in normotensive and pre-eclamptic women was 116.19 ± 9.91 and 145.75 ± 5.50 mmHg, respectively, and the mean diastolic blood pressure in normotensive and pre-eclamptic women recorded was 69.26 ± 7.68 and 91.00 ± 151 mmHg, respectively.

The value of mean ACR among normotensive and pre-eclampsia group is shown in Table 1. The ACR value of PE subjects was relatively higher than that of the normotensives with statistical significant difference. The cut-off value of ACR was taken as 35.5 mg/mmol as in previous study [9].

Table 1 shows a statistical significant difference of mean ACR value between normotensive and pre-eclamptic women with higher value in the latter group. The number of women according to test positivity and negativity is shown in Table 2. The association of ACR with pre-eclampsia is shown in Table 3.

Table 1 Distribution of urinary ACR among normotensive and pre-eclamptic women

Urinary ACR	Normotensive ($N = 54$)	Pre-eclamptic ($N = 8$)
Mean ± SD	19.26 ± 7.99	51.95 ± 18.78
Range	5.28, 37	22.94, 81.81
Median	18.63	51.51
Mean difference	32.69	
P value	<.01*	

* Statistically significant

Table 2 Distribution of women according to test positivity

Test used in study	Test positive (*N*)	Test negative (*N*)	Total (*N*)
ACR (≥35.5 mg/mmol)	9 (14.52%)	53 (85.48%)	62 (100%)

Table 3 Association of ACR with pre-eclampsia

ACR	Normotensive (*N*)	Pre-eclampsia (*N*)	Total (*N*)
Test positive	2 (3.23%)	7 (11.29%)	9 (14.52%)
Test negative	52 (83.87%)	1 (1.61%)	53 (85.48%)
Total	54 (87.10%)	8 (12.90%)	62 (100%)

Tables 2 and 3 show that among total ACR positive 9 (14.52%) women, 7 (11.29%) women developed PE later on in pregnancy and only 2 (3.23%) women remain normotensive, whereas among total ACR test negative 53 (85.48%) women only 1 (1.61%) woman developed PE. For pre-eclampsia screening, in early pregnancy, spot ACR cut-off ≥35.5 mg/mol has sensitivity of 87.5%, specificity of 96.30%, PPV of 77.78% and NPV of 98.11%.

Discussion

Pre-eclampsia is a leading cause of maternal and foetal mortality and morbidity. The molecular mechanisms underlying pre-eclampsia have been described in the recent years. Previous studies have shown that altered regulation and signalling of angiogenic pathways contribute to the inadequate cytotrophoblast invasion in pre-eclampsia. Endothelial dysfunction can occur as early as 22 weeks of gestation [6]. Microalbuminuria, a marker of endothelial dysfunction, might also be apparent by this time, although at a level undetectable by immunochemical methods. Although a 24-h collection of urine for estimation of albumin is the gold standard, a single spot urinary ACR was used in this study because it is more feasible in clinical practice as a screening test and 24-h collection would have

been more time-consuming and cumbersome. Some, but not all past studies have shown an excellent correlation between a spot urinary ACR and albumin excretion in a 24-h urine sample in normal pregnancy and pre-eclampsia [10].

The incidence of pre-eclampsia in our study group is 12.90% which is comparable to the incidence of 4–18% in developing countries [2]. We found that the spot urinary ACR at 20–28 weeks of gestation was significantly higher in women who subsequently developed pre-eclampsia with mean value of 51.95 ± 18.78 mg/mmol and then in those who remain normotensive with mean value of 19.26 ± 7.99 mg/mmol. Baweja et al. [9] and Fatema et al. [11] found the similar results in their studies. The sensitivity of ACR at cut-off value of ≥35.5 mg/mmol as screening test to predict pre-eclampsia in our study was found to be 87.5% which is comparable to the studies done by Baweja et al. [9] (83.3%) and Fatema et al. [11] (80%). The specificity (96.30%), PPV (77.78%) and NPV (98.11%) derived in our study are high and can be compared to the earlier studies [12]. Shaarawy [13] found that microalbuminuria at 10–12 weeks of gestation had 50% sensitivity, 58% specificity, 50% PPV and a 91% NPV for the later development of pre-eclampsia. These statistical analysis shows that spot urinary ACR has good predictive role as screening test for pre-eclampsia in early pregnancy. Therefore, spot urinary protein/creatinine ratio or urinary albumin/creatinine ratio (ACR) has been advocated as an alternative in various studies [14].

Conclusions

Our study inferred that single spot urinary ACR values are higher in early pregnancy in asymptomatic women who developed pre-eclampsia later on. When measured early in the second trimester, an ACR ≥ 35.5 mg/mmol predicted pre-eclampsia well before the onset of clinical manifestations with high sensitivity of 87.5% and specificity of 96.30%. So, it can be used as a good screening tool for predicting pre-eclampsia in early pregnancy. A small sample size is the limitation of our study, and study of larger sample size is recommend before making spot urinary protein/creatinine ratio a routine screening test.

Compliance with Ethical Standards

Conflict of interest Vineet Mishra, Preeti Goyal, Priyankur Roy, Sumesh Choudhary, Rohina Aggarwal, Khushali Gandhi, Bhumika Vyas and Shaheen Hokabaj declare that they have no conflicts of interest.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

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